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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/795,790 | 03/08/2004 | Arindam Roy | NVI 5268.2 | 7703 |

321. 7590 10/03/2006

SENNIGER POWERS
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS, MO 63102

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| EXAMINER |
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SAUCIER, SANDRA E

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| ART UNIT | PAPER NUMBER |
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1651

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/795,790

Applicant(s)

ROY ET AL.

Examiner

Sandra Saucier

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 14, 17, 18, 23, 24, 26, 34, 36, 41, 45 and 50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>6/21/04, 9/15/04</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 1-5,14,17,18,21-24,26,34,36,41,45,50,56-58,66-68,73,77,82,88,92,97,101,102,106,113,114,120,126,130,134,145-147,150-152 and 155-187.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 21,22,56-58,66,68,73,77,82,88,92,96,97,101,102,113,114,120,126,130,134,145-147,150-152 and 155-187.

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DETAILED ACTION

Claims 1-5, 14, 17, 18, 21-24, 26, 34, 36, 41, 45, 50, 56-58, 66-68, 73, 77, 82, 88, 92, 96, 97, 101, 102, 106, 113, 114, 120, 126, 130, 134, 145-147, 150-152, 155-187 are pending. Claims 1-5, 14, 17, 18, 23, 24, 26, 34, 36, 41, 45, 50 are considered on the merits. Claims 21, 22, 56-58, 66-68, 73, 77, 82, 88, 92, 96, 97, 101, 102, 106, 113, 114, 120, 126, 130, 134, 145-147, 150-152, 155-187 are withdrawn from consideration as being drawn to a non-elected invention.

Election/Restriction

Claims 21, 22, 56-58, 66-68, 73, 77, 82, 88, 92, 96, 97, 101, 102, 106, 113, 114, 120, 126, 130, 134, 145-147, 150-152, 155-187 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made without traverse in Paper No. 9/15/06.

Information Disclosure Statement

The listing of the references on PTO 1449 is incomplete. A proper citation includes AUTHOR, TITLE, JOURNAL, VOLUME, NUMBER, INCLUSIVE PAGES, (month), YEAR. Citation 19 is missing the author and title of the article, journal name.

MPEP37 CFR 1.98(b) requires that each U.S. patent listed in an information disclosure statement be identified by patentee, patent number, and issue date. Each foreign patent or published foreign patent application must be identified by the country or patent office which issued the patent or published the application, an appropriate document number, and the publication date indicated on the patent or published application. Each publication must be identified by author (if any), title, relevant pages of the publication, date and place of publication. The date of publication supplied must include at least the month and year of publication, except that the year of publication (without the month) will be accepted if the applicant points out in the information disclosure statement that the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of

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publication is not in issue. The place of publication refers to the name of the journal, magazine, or other publication in which the information being submitted was published.

Claim Rejections – 35 USC § 112

INDEFINITE

Claims 2-5, 14, 17, 18, 24, 26, 34, 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 has no antecedent basis for "a heterogeneous catalyst". Please amend to state wherein the enantioselective enzyme is immobilized on a solid support", or some such recitation.

Claims 3, 14, 17, 18, 50 are further process steps, but are in passive language instead of active language which is more suitable for process steps (withdrawing, contacting, racemizing, recycling, etc.)

Claims 24, 26 use the convention D, L for designation of the isomers of α -hydroxy acid/ester. However, this designation is used for amino acids, sugars and does not correspond to the conventional R, S nomenclature nor does it necessarily correspond to optical rotation conventions d,l or +,-. Since the substrates are not limited to amino acids or amino acid derivatives, the use of this nomenclature is confusing.

Claim 34 states that the process is limited to substrates which are the α -hydroxy analogs of methionine and lysine. However, the independent claim includes a phosphorus group and cannot be such an analog since neither methionine nor lysine contain one. The dependent claim does not find antecedent basis in the independent claim.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action: A person shall be entitled to a patent unless (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign

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country, before the invention thereof by the applicant for a patent, (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by US 5,580,783 [A].

The claims are directed to an enantioselective process of hydrolyzing an α -hydroxy substituted carboxylic acid ester using *C. antarctica* lipase.

US 5,580,783 discloses an enantioselective hydrolytic process using lipase on α -hydroxy carboxylic acids. See col. 2, formula I where R3 may be OH, R1 and R2 are each phenyl C1-C6. A lipase particularly useful in this process is from *C. antarctica* (col. 6, ls. 45-53). Example 3 exemplifies the use of lipase from *C. antarctica* to enantioselectively hydrolyze an α -substituted hydroxy carboxylic acid ester which falls within the structure of claim 1.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action: (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 23, 24, 26, 34, 41, 45, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/40438 [24] or US 5,580,783 [A] or US 5,248,610 [B] in combination with Cambou *et al.* [U] and Jones [V].

The claims are directed to an enantioselective process of hydrolyzing an α -hydroxy substituted carboxylic acid ester using porcine pancreatic lipase, A.

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niger lipase or *C. antarctica* lipase.

The references are relied upon as explained below.

US 5,580,783 discloses an enantioselective hydrolytic process using lipase on α -hydroxy carboxylic acids. See col. 2, formula I where R3 may be OH, R1 and R2 are each phenyl C1-C6. A lipase particularly useful in this process is from *C. antarctica* (col. 6, ls. 45-53).

WO 02/40438 discloses a method for enantioselectively hydrolyzing carboxylic acid esters using enzymes. The enzymes may especially be lipases or esterases. Particularly useful are porcine pancreatic lipase (PPL), lipase from *C. antarctica* (CAL-A, CAL-B), lipase from *Aspergillus niger* (ANL) (page 11). The compounds are of formula 1, where $n=0$ and Y=hydrogen. The enzymes may be immobilized (page 12).

US 5,248,610 disclose a method of producing optically active α -hydroxyesters using a transesterification process employing lipase from *A. niger*, porcine pancreatic lipase and others (Table col. 4). This demonstrates that these lipases are catalytically competent to resolve enantiomers of α -hydroxy carboxylic acids.

Cambou *et al.* disclose various strategies for lipase-catalyzed resolution of racemic acids, namely hydrolysis, esterification or transesterification. The same lipase can be used for the three strategies. Asymmetric hydrolysis is considered to be the superior resolution strategy for racemic acids.

Jones teach that the same enzyme transforms similar substrates with the same regio- and stereospecificity (page 3353).

The use of CAL or ANL or PPL for the resolution of α -hydroxy racemic acids in the method of US 5,580,783 or WO 02/40438 would have been obvious when taken with US 5,248,610 in view of Cambou *et al.* because all

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three of these lipases have been used in the prior art to resolve α -hydroxy carboxylic acids. Thus, the broad specificity of these lipases towards α -hydroxy carboxylic acids is well known, particularly with the teaching of Jones that the same enzyme transforms similar substrates.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/40438 [24], US 5,580,783 [A], US 5,248,610 [B], Cambou *et al.* [U], Jones [V] as applied to claims 1, 23, 24, 26, 34, 41, 45, 50 above, and further in view of Fadnavis *et al.* [28].

The claim is further drawn to the use of an immobilized lipase.

Fadnavis *et al.* disclose the immobilization of enzymatic catalysts in alginate.

The use of the immobilization technique disclose by Fadnavis *et al.* in an alginate/gelatin blend in the methods of WO 02/40610 or US 5,580,783 would have been obvious because Fadnavis *et al.* disclose the superior properties of such gels for lipase immobilization particularly in view of the teaching in WO 02/40438 where lipase immobilization is suggested (page 12).

Claim 3-5, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/40438 [24], US 5,580,783 [A], US 5,248,610 [B], Cambou *et al.* [U], Jones [V], Fadnavis *et al.* [28] as applied to claims 1, 2, 23, 24, 26, 34, 41, 45, 50 above, and further in view of Flickinger *et al.* [W] or Balcao *et al.* [27].

The claims are further drawn to continuous or intermittent stock introduction with continuous or intermittent withdrawal of product from a fixed bed reactor.

Flickinger *et al.* in the Encyclopedia of Bioprocess Technology, discloses various reactors for immobilized enzymes including fixed-bed reactors, continuous feed reactors, batch reactors, etc. page 1066.

Balcao *et al.* is a review which discloses the state of the art in 1996 in the operation of bioreactors with immobilized lipases. Packed bed reactors where the substrate is flowed through the bed is well known. Continuous or intermittent feeding of the substrate with continuous or intermittent withdrawal of the products is also known (see continuous stirred reactors, fixed bed reactors, discussed on page 407).

The use of either a continuous or intermittent flow reactor with immobilized enzymes in the method of WO 02/40610 or US 5,580,783 would have been obvious because these are well known in the art as evidence by Balcao *et al.* or Flickinger *et al.*.

Claims 17, 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/40438 [24], US 5,580,783 [A], US 5,248,610 [B], Cambou *et al.* [U], Fadnavis *et al.* [28], Jones [V], Flickinger *et al.* [W], Balcao *et al.* [27] as applied to claims 1-5, 14, 23, 24, 26, 34, 41, 45, 50 above, and further in view of Kirk-Othmer [X].

The claims are further drawn to extraction of the product with two solvents (partitioning).

The Kirk-Othmer Encyclopedia of Separation Technology discloses different types of liquid-liquid extraction. On page 774, fractional extraction with two solvents (7b) is explained.

The fractionation of the product with an organic solvent and an aqueous solvent in the method of WO 02/40610 or US 5,580,783 would have been obvious because such separations are routine in the art. WO 02/40438 also teach that the unprotonated acid is soluble in water while the unreacted ester is soluble in organic solvent (page 16).

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/40438 [24], US 5,580,783 [A], US 5,248,610 [B], Cambou *et al.* [U],

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Fadnavis *et al.* [28], Jones [V], Flickinger *et al.* [W], Balcao *et al.* [27], Kirk-Othmer [X] as applied to claims 1-5, 14, 17, 23, 24, 26, 34, 36, 41, 45, 50 above, and further in view of Hirohara [U2] or Hirose [V2] or US 6,620,600 [C].

The claims are further directed to racemization of the unreacted ester and recycling of the racemized ester into the reactor.

The recycling of the unwanted enantiomer by racemization is well known in the art as evidenced by the reviews of Hirose or Hirohara or US 6,620,600 where such recycling by racemization is taught. Thus, it would have been obvious to racemize the unwanted enantiomer and recycle it in the method of WO 02/40438 or US 5,580,783.

All of the elements of the claimed method are known in the art of biotransformation. In the absence of evidence to the contrary or unexpected results, no claim is allowed.

One of ordinary skill in the art would have been motivated at the time of invention to make these substitutions and additions in order to obtain the resulting compound as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such

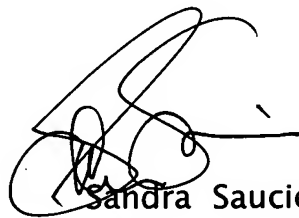
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copending claims is requested in response to the office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday, Tuesday, Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Sandra Saucier', is written over a circular stamp or seal.

Sandra Saucier

Primary Examiner

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September 27, 2006